

CLINICAL RESEARCH

Clinical Trial

Does Microvolt T-Wave Alternans Testing Predict Ventricular Tachyarrhythmias in Patients With Ischemic Cardiomyopathy and Prophylactic Defibrillators?

The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) Trial

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Objectives

The purpose of this trial was to determine whether microvolt T-wave alternans (MTWA) predicts ventricular tachyarrhythmic events (VTEs) in post-myocardial infarction patients with left ventricular ejection fraction (LVEF) $\leq 30\%$.

Background

Previous studies have established MTWA as a predictor for total and arrhythmic mortality, but its ability to identify prophylactic implantable cardioverter-defibrillator (ICD) recipients most likely to experience VTEs remains uncertain.

Methods

This prospective trial was conducted at 50 U.S. centers. Patients were eligible if they met MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) indications for device implant. All patients underwent MTWA testing followed by ICD implantation, with pre-specified programming to minimize the likelihood of therapies for non-life-threatening VTE. Minimum follow-up was 2 years with annual MTWA testing. Initially indeterminate MTWA tests were repeated.

Results

Analyses were conducted on 575 patients (84% male; average age \pm SD = 65 ± 11 years; average LVEF \pm SD = 0.24 ± 0.05). The final distribution of MTWA results were: MTWA positive in 293 (51%), MTWA negative in 214 (37%), and indeterminate in 68 patients (12%). Over an average follow-up of 2.1 ± 0.9 years, there were 70 VTEs. A VTE occurred in 48 of 361 (13%, 6.3%/year) MTWA non-negative and 22 of 214 (10%, 5.0%/year) MTWA negative patients. A non-negative MTWA test result was not associated with VTE (hazard ratio: 1.26; 95% confidence interval: 0.76 to 2.09; $p = 0.37$), although total mortality was significantly increased (hazard ratio: 2.04; 95% confidence interval: 1.10 to 3.78; $p = 0.02$).

Conclusions

In MADIT-II-indicated ICD-treated patients, the risk of VTE does not differ according to MTWA classification, despite differences in total mortality. (MASTER I-Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients; NCT00305240) (J Am Coll Cardiol 2008;52:1607-15) © 2008 by the American College of Cardiology Foundation

Despite increased deployment of implantable cardioverter-defibrillators (ICDs) guided by prospective clinical trial data (1-4), prevention of sudden cardiac death (SCD) remains

an unmet challenge. From a public health perspective, SCD continues to be the leading source of mortality in developed countries, with approximately 310,000 annual deaths occurring in the U.S. (5). At the same time, the economic burden of broad ICD deployment is substantial (6). Therefore, identification of high-risk patients most likely to benefit from ICD implantation is of significant clinical and health policy interest. Whereas current device implant guidelines focus on patients with reduced left ventricular ejection fraction (LVEF) ($\leq 30\%$ to 35%), this approach lacks specificity for SCD. In principle, improved risk stratification techniques could more accurately identify high-risk patients who would benefit from ICD therapy, thereby reducing the number of unnecessary ICD implantations and diminishing the financial burden to the health care system.

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Abbreviations and Acronyms

CHF = congestive heart failure

CI = confidence interval

CRT = cardiac resynchronization therapy

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

MTWA = microvolt T-wave alternans

NYHA = New York Heart Association

SCD = sudden cardiac death

VTE = ventricular tachyarrhythmic event

Measurement of microvolt T-wave alternans (MTWA) during controlled heart rate elevation has emerged as a potentially useful predictor of ventricular arrhythmic events and mortality (7), including in post-myocardial infarction patients (8) and those with ischemic cardiomyopathy (9) or congestive heart failure (CHF) (10). Whether application of MTWA can further improve risk stratification in patients with low LVEF who are currently considered candidates for prophylactic ICD therapy is unclear. Specifically, MTWA might identify a subgroup of this patient population at sufficiently low risk of SCD in which ICD therapy might be withheld. The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients) trial was a prospective, multicenter, industry-supported (Medtronic Inc., Minneapolis, Minnesota) trial conducted in the U.S. in which patients meeting "MADIT-II" indication for ICD treatment (11) underwent MTWA testing before device implantation. This trial primarily recruited ambulatory outpatients from within private practices. The primary objective was to determine whether MTWA testing predicted subsequent development of ventricular tachyarrhythmic events (VTEs).

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Methods

Patient recruitment. The MASTER trial was conducted by 50 participating U.S. investigator centers (82% private practice, 18% academic medical center). The protocol was approved by an institutional review board for each participating center. Patient recruitment, data acquisition, and follow-up were the responsibility of the local investigators and overseen by MASTER trial personnel. All data were sent to the central data analysis and coordinating center (Medtronic Cardiac Rhythm Disease Management Clinical Research Department), which was responsible for review, processing, and analysis of data as well as coordination with the independent Clinical Events Committee and MTWA reading core laboratory (Massachusetts Institute of Technology, Division of Health Sciences and Technology). The first patient was enrolled in October 2003, with completion of follow-up in February 2007 and database closure in May 2007.

Patients were candidates for enrollment if they had a prior myocardial infarction, LVEF $\leq 30\%$, were ≥ 18 years old, and were able to give informed consent. Trial exclusions included: atrial fibrillation or flutter at time of enrollment, documented sustained or symptomatic ventricular tachyarrhythmia (including a history of cardiac arrest), myocardial infarction within the past month, revascularization procedure (surgical or percutaneous) within the past 3 months, diagnostic electrophysiology study or MTWA test within the past year, class IV CHF, advanced cerebrovascular disease, life expectancy of <1 year, inability to perform MTWA testing, or contraindication to ICD implantation.

Baseline patient demographic, clinical, and medication data were acquired upon trial enrollment.

MTWA testing. Baseline MTWA testing was required for all enrolled patients. Treadmill was the only method of exercise testing used. For patients unable to exercise, other methods were used, including dobutamine infusion and cardiac pacing. All sites were required to use either the CH2000 or HearTwave system (Cambridge Heart Inc., Bedford, Massachusetts) for MTWA testing. All sites were trained and certified by a Cambridge Heart Inc. representative before enrollment of patients.

Standard criteria were applied to MTWA interpretation (12). In brief, a test was considered positive if $>1.9 \mu V$ of alternans was recorded in either 1 orthogonal lead or 2 contiguous pre-cordial leads with an onset heart rate of ≤ 110 beats/min during a 2-min recording period that was free from significant artifacts. A test was considered negative if the aforementioned criteria were not met with a maximum negative heart rate of ≥ 105 beats/min. All other successfully completed tests were considered indeterminate—generally a result of excessive electrode noise, inability to achieve target heart rate, frequent ectopic beats, or other artifacts.

The protocol required that all indeterminate MTWA tests be repeated. If the repeat MTWA test yielded a determinate result (positive or negative), the determinate result was used for trial analysis. A new MTWA test classification called "technically inadequate" was established to denote any test in which either the MTWA data were not acquired (e.g., "leads off" indicated by the machine) or the initial classification was indeterminate and the test was not repeated (unless medical justification was supplied). Technically inadequate tests were excluded from analysis. All MTWA tests were over-read by a core laboratory blinded to patient characteristics. The core laboratory classification was considered final.

In accordance with common practice, the protocol specified combining positive and indeterminate outcome patients into a single MTWA "non-negative" group that was compared against MTWA negatives for primary trial outcome analysis. This approach has been validated by studies showing equivalent outcomes among MTWA positives and indeterminates (9). The MASTER protocol additionally required follow-up MTWA testing every 12 months after enrollment until trial completion. Repetition of initially indeterminate MTWA tests was required for baseline and follow-up MTWA testing. For consistency, sites were encouraged to use the same method of heart rate elevation

(e.g., exercise, cardiac pacing, or pharmacologic) on the follow-up tests as was used for the baseline test.

Device implantation and programming. In accordance with practice guidelines, clinically indicated market-approved Medtronic ICDs were to be subsequently implanted in all patients enrolled in the MASTER trial. Single-chamber, dual-chamber, and resynchronization devices were all allowable.

To minimize the likelihood of therapies for non-life-threatening ventricular arrhythmias, the protocol required the following device programming: ventricular fibrillation (VF) detection interval: 320 ms; VF number of intervals to detect: 24 of 32; ventricular tachycardia detection interval: 370 ms (monitor only); ventricular tachycardia number of intervals to detect: 16; supraventricular tachycardia (SVT) discriminators “on;” SVT limit: 300 ms with high-rate time out disabled; maximum output shocks across all VF therapies; and pre-storage electrogram “on.” Antitachycardia pacing therapies were not permitted. Deviations from the aforementioned programming required medical justification from the participating site. The proportion of patients programmed according to protocol specifications was 88% at baseline and 95% by the 6-month follow-up visit.

Trial follow-up and end point determination. Patients were followed at 6-month intervals for a minimum of 2 years and up to 4 years or until trial closure. Device, clinical, and medication data were reviewed and updated during routine trial visits. In addition, patient diaries were supplied to facilitate patient recall of symptoms and correlation with device-recorded arrhythmias. Hospital stays or clinician visits for any end point events were noted.

The primary end point for the MASTER trial was a VTE, defined as: 1) SCD; or 2) an appropriate ICD discharge by a device programmed in accordance with the trial protocol. All ventricular tachyarrhythmic episodes recorded by the devices and deaths were adjudicated by an independent Clinical Events Committee physician blinded to patient characteristics and MTWA test results. SCD was defined as a cardiac death within 1 h of onset of symptoms or occurring during sleep in the absence of a more plausible explanation.

Statistical analyses. The trial was designed to detect a hazard ratio (HR) of 3 between the MTWA non-negative group and the MTWA negative group. A minimum of 57 VTEs were required to achieve at least 80% power with a type I error of 0.05. All statistical analyses were performed with SAS (version 9.1, SAS Institute Inc., Cary, North Carolina). Baseline characteristics between MTWA negative and non-negative groups were compared with Student *t* tests for continuous variables and chi-square tests for categorical variables. Survival curves between the MTWA negative and non-negative groups were constructed with Kaplan-Meier estimates (13). Cox proportional hazards models (14) were used to assess the relationship between MTWA testing and VTE and to estimate the HRs and 95% confidence intervals (CIs). Cox regression analysis was

used to adjust for pre-specified potential confounding variables, which included: age, gender, LVEF, beta-blocker drugs, positive inotropic agents, QRS duration, race, and New York Heart Association (NYHA) functional class. All statistical tests were 2-sided and used an alpha level of 0.05.

Results

Baseline characteristics. The trial enrolled 654 patients, of whom 44 were later found to have met study exclusion criteria and 35 did not have a valid baseline MTWA test (21 defined as technically inadequate according to the protocol and 14 not performed). The remaining 575 patients used for analyses consisted of 361 (63%) MTWA non-negative patients (293 [51%] positive and 68 [12%] indeterminate) and 214 (37%) MTWA negative patients. The distribution of testing modality was 78% exercise, 10% pharmacological, 7% atrial pacing, and 5% atrioventricular sequential pacing. Table 1 provides the baseline characteristics of MASTER trial patients. The population was, on average, 65 years old and 84% male with a mean LVEF of 24%. In addition, 50% had a QRS duration ≥ 120 ms, and 71% had NYHA functional class II to III CHF. Some significant differences existed between MTWA negative and non-negative groups. The MTWA non-negative patients were significantly older, less frequently Caucasian, less likely to be taking beta-blocker drugs, and had wider QRS durations.

Trial outcomes. There were 70 VTEs over a mean of 2.1 ± 0.9 years (7 SCDs and 63 appropriate device therapies). A VTE occurred in 48 MTWA non-negative and 22 MTWA negative patients. The annual event rates for MTWA non-negative and negative patients were 6.3% and 5.0%, respectively (HR: 1.26; 95% CI: 0.76 to 2.09; $p = 0.37$). Kaplan-Meier event-free survival curves for VTE according to MTWA classification are shown in Figure 1. After multivariate adjustment, MTWA remained nonpredictive of VTE (HR: 1.16; 95% CI: 0.68 to 1.99; $p = 0.58$). Although tests classified as technically inadequate were excluded from analysis, inclusion of these patients within the MTWA non-negative cohort did not alter this result.

Additional outcomes measures were explored in secondary analysis (Table 2). Total mortality was significantly greater in MTWA non-negative patients (HR: 2.04; 95% CI: 1.10 to 3.78; $p = 0.02$) (Fig. 2), a finding that remained statistically robust after multivariate adjustment (HR: 2.16; 95% CI: 1.13 to 4.12; $p = 0.02$).

Other predictors of VTE. Univariate Cox proportional hazards analysis was used to evaluate other potential variables for VTE prediction. Beta-blocker treatment was associated with a significantly decreased frequency of VTE (HR: 0.54; CI: 0.30 to 0.96; $p = 0.04$), whereas spironolactone treatment was associated with an increased frequency of this end point (HR: 1.68; 95% CI: 1.00 to 2.80; $p = 0.048$). The LVEF was also significantly associated with VTE (HR: 0.95; 95% CI: 0.90 to 0.99; $p = 0.02$). Each 1% decline in LVEF was associated with a 5% relative

Table 1 Baseline Characteristics

Characteristics	All (n = 575)	MTWA Negative (n = 214)	MTWA Non-Negative (n = 361)	p Value*
Age, yrs	65 ± 11	63 ± 11	66 ± 10	0.006
Gender, % male	84	81	86	0.12
Race, % white	89	94	86	0.004
LVEF, %	24.0 ± 4.8	24.4 ± 4.5	23.8 ± 4.9	0.11
QRS ≥120 ms, %	50	44	55	0.01
LBBB†	36	42	34	0.21
RBBB†	18	15	19	0.45
IVCD†	25	23	25	0.69
QRS measurement (ms)	119 ± 30	115 ± 30	121 ± 29	0.02
CHF, %	73	74	72	0.51
History of atrial fibrillation, %	18	19	17	0.61
CABG, %	55	52	57	0.28
PCI, %	52	55	50	0.20
Diabetes, %	35	34	36	0.65
Hypertension, %	68	64	70	0.12
Syncope, %	12	14	11	0.44
Device type, %				0.34
Single-chamber	37	41	35	
Dual-chamber	40	37	41	
CRT	23	22	25	
NYHA functional class, %				0.57
I	15	15	14	
II	44	46	42	
III	27	26	27	
No HF	15	13	17	
Medications, %				
Aspirin	78	78	78	0.99
ACE	64	64	65	0.99
ARB	19	20	18	0.49
Beta-blocker	87	92	86	0.01
Statin	78	81	76	0.24
Digoxin	23	20	25	0.11
Diuretic	62	59	63	0.28
Spironolactone	21	23	19	0.17
Class I antiarrhythmic	0.2	0	0.3	0.44
Class III antiarrhythmic	7	7	7	0.99

*t tests used for continuous variables and chi-square tests for categorical variables. †Percentages derived from 285 patients with QRS duration ≥120 ms.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CHF = congestive heart failure; CRT = cardiac resynchronization therapy (device type); IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MTWA = microvolt T-wave alternans; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RBBB = right bundle branch block.

increase in VTE. There was borderline evidence for increased VTE among patients with QRS duration ≥120 ms (HR: 1.64; 95% CI: 0.99 to 2.68; $p = 0.05$).

Subgroup analyses. The predictive value of MTWA testing for VTE was evaluated in patient subgroups including LVEF, QRS duration, beta-blocker usage, cardiac resynchronization therapy (CRT), MTWA testing modality, and NYHA functional class (Table 3). The possibility of significant interactions ($p < 0.05$) between MTWA and subgroup variables was evaluated, but none were found. The MTWA prediction did not achieve statistical significance within any subgroup; however, MTWA nearly achieved significant association for VTE within narrow QRS duration (<120 ms) patients (HR: 2.30; 95% CI: 0.92 to 5.76; $p = 0.08$). Finally, restricting primary end point analysis to those patients who had MTWA testing with the exercise

modality did not change the study outcome (HR: 1.14; 95% CI: 0.65 to 2.02).

Indeterminate MTWA tests. The indeterminacy rate after the initial MTWA test was 19%. The predominant causes of indeterminacy for the 107 patients initially classified with an indeterminate test result were: inability to achieve target HR in 32 (30%), frequent ectopic beats in 22 (21%), electrode noise in 15 (14%), and nonsustained alternans in 36 (34%). Of the 107 patients that were initially classified as indeterminate, repeat MTWA testing was performed for 69 patients, yielding a baseline determinate result for 41 (59%). Patient safety concerns precluded repeat testing for 38 patients. Two patients had an initial technically inadequate test that was reclassified as indeterminate on the basis of repeat testing. The causes of indeterminacy for the 68 patients who were ultimately classified as having

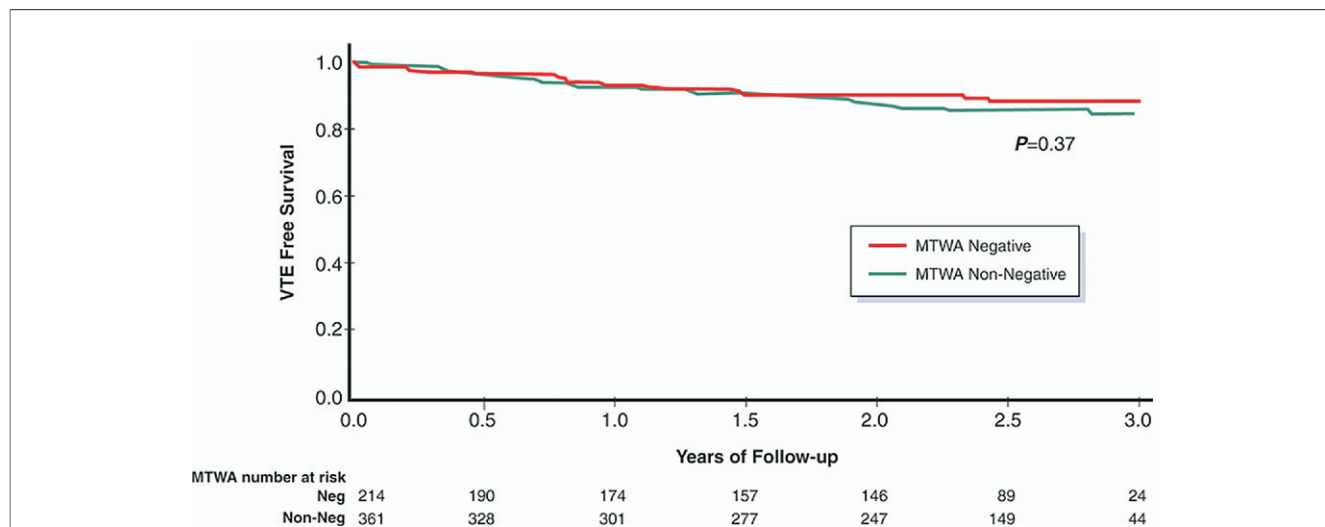


Figure 1 Kaplan-Meier Survival Curves for VTE Free Survival

MTWA = microvolt T-wave alternans; VTE = ventricular tachyarrhythmic event (primary end point).

an indeterminate baseline MTWA test were: failure to reach adequate heart rate in 18 (26%), frequent ectopy in 18 (26%), excessive noise in 25 (37%), RR interval alternans in 6 (9%), and unsustained T-wave alternans in 1 (1%). The HR for VTE when comparing only MTWA positives versus negatives was 1.24 (95% CI: 0.73 to 2.08; $p = 0.43$) and remained nonsignificant after multivariate adjustment. Table 4 depicts comparisons between individual MTWA cohorts and VTE occurrence. There were no significant differences in VTE between individual MTWA groups.

After initiation of the MASTER trial, a retrospective analysis of the T-Wave Alternans in Heart Failure Study concluded that more accurate MTWA classification is achieved by considering as abnormal only those indeterminates that are due to patient-related factors, including excessive ectopy, inability to reach target HR, or nonsustained alternans (15). Using this modified MTWA classification algorithm had little effect on the univariate HR estimate for VTE (HR: 1.34; 95% CI: 0.80 to 2.25; $p = 0.27$).

Discussion

The objective of the MASTER trial was to determine whether MTWA predicts VTE in post-myocardial infarction patients with LVEF $\leq 30\%$. Over an average follow-up of 2.1 years, there was no observed correlation between MTWA result and VTE. Specifically, the VTE rate was not significantly lower in the MTWA negative group than in the MTWA non-negative group. Additionally, Kaplan-Meier analysis showed no divergence in this end point between MTWA groups at any time during the trial. Because enrolled patients were to receive ICDs by design, 90% of end point events were appropriate ICD therapies and 10% were sudden deaths. Therefore, the MASTER trial demonstrates that MTWA testing does not identify MADIT-II–indicated patients more (or less) likely to receive appropriate ICD therapies.

The MASTER trial is among the largest prospective evaluations to date of MTWA in MADIT-II–like patients. Other strengths include uniform treatment with ICDs and

Table 2 Trial Outcome Events

Outcomes, n (%)	MTWA Negative (n = 214)	MTWA Non-Negative (n = 361)	Unadjusted HR (95% CI)	p Value*
First VTE	22 (10.3)	48 (13.3)	1.26 (0.76–2.09)	0.37
Appropriate device therapy	20 (9.9)	43 (9.6)	1.24 (0.73–2.11)	0.42
Sudden cardiac death	2 (9.1)	5 (10.4)	1.44 (0.28–7.44)	0.66
Total mortality	13 (6.1)	46 (12.7)	2.04 (1.10–3.78)	0.02
Sudden cardiac	3 (23.1)	7 (15.2)	1.35 (0.35–5.23)	0.66
Nonsudden cardiac	5 (38.5)	17 (37.0)	1.96 (0.72–5.31)	0.19
Noncardiac	3 (23.1)	15 (32.6)	2.88 (0.83–9.94)	0.10
Unknown	2 (15.4)	7 (15.2)	2.02 (0.42–9.72)	0.38

*p values are based on Wald's test with estimates from the Cox proportional hazard models.

CI = confidence interval; HR = hazard ratio; MTWA = microvolt T-wave alternans; VTE = ventricular tachyarrhythmic event (primary end point).

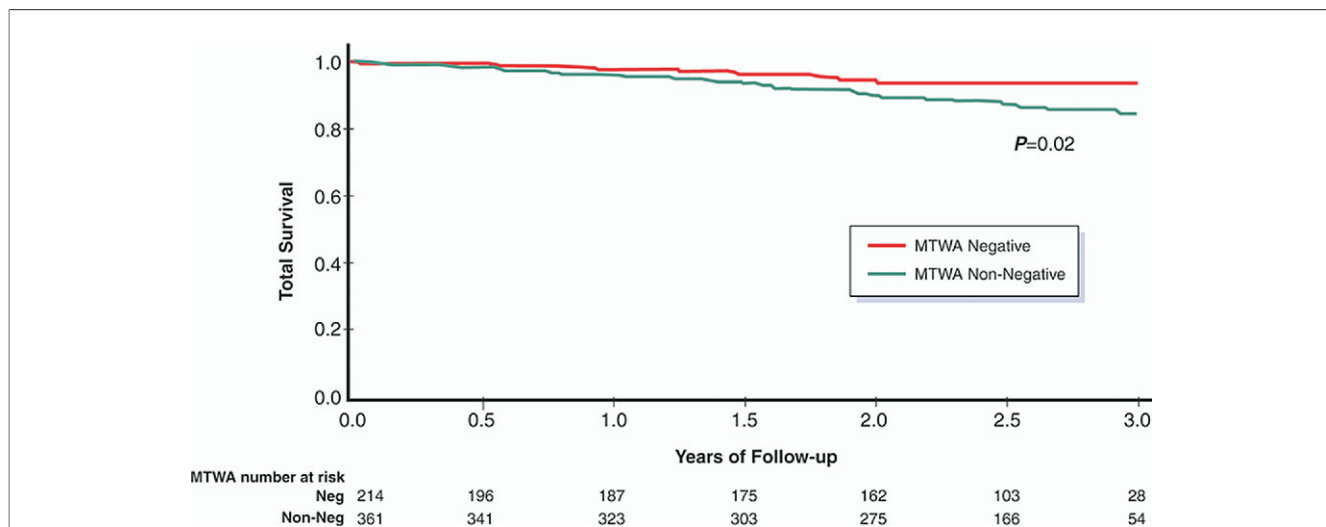


Figure 2 Kaplan-Meier Survival Curves for Total Mortality

MTWA = microvolt T-wave alternans.

standardization of device programming to minimize shocks for nonlethal arrhythmias. In addition, our MTWA indeterminacy rate of 12% is among the lowest reported and was achieved through repeat testing of initially indeterminate tests. Many prior studies of MTWA testing in MADIT-II- (16,17) or SCD-HeFT-like post-myocardial infarction patients (9,18) have had significant limitations, including: few enrolling centers (9,18), small study size (16,17), retrospective design (17), lack of standardized ICD treatment or device programming (9,16–18), and higher indeterminacy rates (9,16–18). The MASTER trial overcomes these limitations and is among the most carefully controlled prospective MTWA trials.

The MASTER trial's findings are consistent with some recent prospective studies of MTWA testing in low-LVEF patients, including the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) MTWA substudy (19) and the CARISMA (Cardiac Arrhythmias and Risk Stratification after Myocardial Infarction) study (20). Additional recent studies that were technically "positive" for MTWA prediction at the same time suggested potential limitations of this technique, namely: 1) MTWA prediction might be limited to 1 year (21); 2) residual arrhythmic risk in MTWA normals might still be substantial (22); and 3) MTWA prediction might be reduced in patients with LVEF <30% (23). In contrast, the aforementioned studies have all included a large percentage of ICD-treated patients and used device-treated or recorded arrhythmias as end points. Hence, the nonspecificity of device end points for arrhythmic death could potentially influence study results by overestimating true SCD events, including in MTWA normal patients. This argument would seem to be supported by the observation that studies with relatively few ICD-treated patients (10,16,24) or ICD shock end points (9) or

in which total mortality was the primary end point (9,10,16) have generally shown MTWA to be a significant predictor of events. The presence of the ICD could also mask association of MTWA with VTE if it facilitates electrical instability through cardiac pacing. However, although device-triggered ventricular arrhythmias do occur, they are uncommon (1%) and thus unlikely to have influenced the results of the MASTER trial (25).

The MASTER trial showed that MTWA was a significant predictor of total mortality (HR: 2), even within a population uniformly treated with ICDs and where 80% of deaths were not sudden cardiac. This HR is similar to the one presented in a study by Chow et al. (9) of ischemic SCD-HeFT type patients (HR: 2.2) but less robust than that reported by Bloomfield et al. (16) of MADIT-II-type patients (HR: 4.8). It seems that some of this excess mortality could be mediated through association of a non-negative MTWA test result with established high-risk clinical features. The MTWA non-negative patients were older (66 vs. 63 years), had wider QRS durations (121 vs. 115 ms), lower beta-blocker exposure (86% vs. 92%), and were less likely to be Caucasian (86% vs. 94%). Although in theory CRT therapy could have influenced results through modifying end point risk after MTWA testing, we did not detect any significant statistical interaction between MTWA prediction and CRT, and prescription of CRT therapy was balanced between MTWA cohorts (Table 1). It is also an intriguing possibility that a non-negative MTWA test might indicate true physiological conditions (e.g., ischemia, CHF, electrolyte disturbances, medication effects) that could impact total mortality independent from ventricular arrhythmia.

According to study protocol, MTWA positives and indeterminates were combined to form a single "non-negative"

Table 3 MTWA Prediction for VTE Within Subgroups

	n	Events	Unadjusted HR (95% CI)	p Value*
LVEF, %				0.71
<25	227	32	1.13 (0.55–2.35)	
≥25	348	38	1.39 (0.69–2.81)	
QRS duration, ms				0.10
≥120	285	43	0.85 (0.45–1.58)	
<120	270	25	2.30 (0.92–5.76)	
Beta-blocker				0.87
Yes	502	56	1.21 (0.70–2.10)	
No	72	14	1.08 (0.30–3.88)	
CRT				0.24
Yes	119	15	0.73 (0.26–2.04)	
No	456	55	1.47 (0.82–2.63)	
MTWA modality†				0.48
Exercise	447	53	1.14 (0.65–2.02)	
Nonexercise	127	17	1.83 (0.60–5.60)	
NYHA functional class				0.41
III	153	24	0.81 (0.36–1.81)	
II	251	24	1.64 (0.68–3.96)	
<II	171	22	1.57 (0.58–4.26)	

*p value for testing the equality of HRs is from Wald's test of interaction between MTWA and each variable with Cox proportional hazard models. †Exercise tests were done with treadmills. Nonexercise test modalities included pharmacological (n = 56), atrial pacing (n = 42), and atrioventricular sequential pacing (n = 29).

Abbreviations as in Tables 1 and 2.

group. This methodology is reflective of common practice and is supported by a large study showing equivalent outcomes among MTWA positives and indeterminates (9). However, during the enrollment period of the MASTER trial, Kaufman et al. (15) published a study suggesting that “patient-related” causes of indeterminacy (excessive ectopy, inability to reach target HR, nonsustained alternans) should be classified as MTWA positive, and “test-related” causes of indeterminacy (electrode noise) should be classified as “technically inadequate” and removed from analysis. Therefore, as a secondary analysis we evaluated the MASTER trial data with this modified MTWA classification algorithm and found that it made no difference to study results. It is worth emphasizing that the impact of this classification algorithm was lessened because the overall indeterminacy rate in the MASTER trial was only 12%.

A previous study suggested that MTWA testing might be confounded by bundle branch block (26). Although statistical testing for interaction between MTWA prediction and bundle branch block was not significant (p = 0.10), the gross correlation of MTWA with VTE in narrow QRS

duration patients was better (HR: 2.30) than in wide QRS duration patients (HR: 0.85) (Table 3). Although this finding is intriguing, this trial was not powered for subgroup analysis.

Another interesting finding in the MASTER trial is the low annual event rates—4.9% total mortality and 5.2% appropriate ICD discharge rate. By comparison, the MADIT-II trial (2), around which our enrollment criteria were based, reported annual mortality and shock rates of 8.5% and 14.1%, respectively, for patients randomized to ICD (although ICD programming was not protocol-specified in that study). Our event rates were more comparable to the SCD-HeFT trial (1), which reported annual mortality and shock rates of 5.8% and 5.1%, respectively. The qualifying LVEF for SCD-HeFT was 35% compared with 30% for MASTER and MADIT-II. We believe the difference in the ICD therapy rate between MASTER and MADIT-II can be explained in large part by the strict ICD programming criteria that was applied to our protocol. The reason for the difference in total mortality between these studies, though, is less clear. Potential explanations include use of higher output devices in MASTER versus MADIT-II; differences in risk profile of patients recruited from private practice (the majority in MASTER) compared with academic hospitals and heart failure clinics; or that, being a recent trial, the reservoir of high-risk patients has been diminished by several years of broad-based prophylactic device implantation. Importantly, as in all MTWA studies, there is likely enrollment bias toward patients with good exercise capacity and exclusion of those with a history of atrial fibrillation, both factors known to influence total and arrhythmic mortality. Finally, the higher use of beta-blocker drugs in our study (87% vs. 70%) could account for some of the difference in event rates. Not only were beta-blocker drugs an independent predictor of freedom from VTE in the MASTER trial, but they have also been shown to suppress MTWA (27). Finally, although the MASTER trial found no association for MTWA predicting the primary end point given sufficient power to detect an HR of ≥3, we cannot exclude the presence of a lesser and potentially clinically relevant association.

The MASTER trial confirmed LVEF to be an important predictor for arrhythmic events. Each 1% decrease in LVEF resulted in a 5% relative increase in the hazard of VTE. However, the substantial differences in total mortality between MASTER, MADIT-II, and SCD-HeFT ICD-treated pa-

Table 4 Comparison of VTE Between MTWA Positive, Negative, and Indeterminate Groups

	Unadjusted HR (95% CI)	p Value*	Adjusted HR (95% CI)	p Value*
Positive versus negative	1.24 (0.73–2.08)	0.43	1.08 (0.62–1.87)	0.80
Indeterminate versus positive	1.13 (0.54–2.30)	0.77	1.11 (0.53–2.34)	0.78
Indeterminate versus negative	1.17 (0.80–1.73)	0.42	1.22 (0.80–1.86)	0.36

*p values are based on Wald's test with estimates from the Cox proportional hazard models. Variables used for adjusted Cox models: age, gender, LVEF, beta-blocker, positive inotropes, QRS duration, race, and NYHA functional class.

Abbreviations as in Tables 1 and 2.

tients despite similar mean LVEFs (24%, 23%, and 25%, respectively) illustrates the limitations of LVEF alone as a risk stratifier and the need to develop more specific predictors for arrhythmic death. Reductions in SCD attributable to ICD treatment in MADIT and MUSTT (Multicenter Unsustained Tachycardia Trial), in which device implant was guided by electrophysiology study and Holter monitor, were approximately 2 times higher than in the MADIT-II and SCD-HeFT trials in which risk stratification (other than ejection fraction) was not used (1–4). However, the MASTER trial results demonstrate that more studies need to be done to understand the role of MTWA in risk stratification for ICD candidacy and, more generally speaking, the relationship between ICD shocks and lethal events. Future investigation might include the combination of MTWA with other risk stratifiers within a “suite of predictors” approach and exploring new ICD indications within higher LVEF populations. The latter is supported by a recent study that found MTWA testing to be highly predictive within post-myocardial infarction patients having LVEF >40% (HR: 20) (28).

Study limitations. The main limitation of this trial is the use of ICD treatment for ventricular tachycardia/ventricular fibrillation as a surrogate for SCD. An analysis of the DEFINITE (Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation) trial by Ellenbogen et al. (29) showed that ICD shocks overestimated arrhythmic mortality by a factor of 2. Because this limitation is inherent to any ICD trial and because we deemed it unethical to withhold ICD therapy in otherwise indicated patients, we instead addressed this issue through requiring that ICD therapies be delivered only for VTEs that were fast (≥ 188 beats/min) and relatively long-lasting (≥ 24 beats). Although this should increase the specificity of therapies for arrhythmic mortality, it is likely that ICD therapies will still overestimate this end point by some (unknown) degree. It is possible that lack of specificity of ICD therapies for lethal arrhythmias could mask a true relationship of MTWA with arrhythmic mortality; thus the findings might not be applicable to a non-ICD-treated population.

In addition, combining different modalities of MTWA testing (exercise, drug infusion, pacing) could be a limitation if the predictive accuracy of these modalities is not equivalent. However, the majority of patients in the MASTER trial were tested with the same modality (treadmill exercise), and study results were not affected by restricting primary outcome analysis to this subset of patients.

Although every effort was made to establish rhythm truth for tachycardia episodes detected by ICDs, this cannot be known with absolute certainty—more so for single-chamber ICDs in which there is no atrial electrogram to guide diagnosis.

Conclusions

The MASTER trial showed that, within community private practice, MTWA testing in MADIT-II–indicated ICD-

treated patients does not predict subsequent VTEs, although MTWA non-negative patients had significantly higher mortality compared with MTWA negative patients.

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REFERENCES

1. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
2. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83.
3. Buxton AE, Lee KL, Fisher JD, et al. A randomised study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882–90.
4. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary artery disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335:1933–40.
5. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update. *Circulation* 2008;117:e25–146.
6. Zwaninger J, Hall W, Dick A, et al. The cost effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006;47:2310–8.
7. Gehi AK, Stein RH, Metz LD, Gomes JA. Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events: a meta-analysis. *J Am Coll Cardiol* 2005;46:75–82.
8. Ikeda T, Saito H, Tanno K, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. *Am J Cardiol* 2002;89:79–82.
9. Chow T, Kereiakes DJ, Bartone C, et al. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2006;47:1820–7.
10. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:456–63.
11. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Am Coll Cardiol* 2002;40:1703–19.
12. Bloomfield DM, Hohnloser SH, Cohen RJ. Interpretation and classification of microvolt T wave alternans tests. *J Cardiovasc Electrophysiol* 2002;13:502–12.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
14. Cox DR. Regression models and life tables. *J Roy Stat Soc B* 1972;34:187–220.
15. Kaufman EF, Bloomfield DM, Steinman RC, et al. “Indeterminate” microvolt T-wave alternans tests predict high risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;48:1399–404.
16. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. *Circulation* 2004;110:1885–9.
17. Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. *Lancet* 2003;362:125–6.
18. Chow T, Kereiakes DJ, Bartone C, et al. Microvolt T-wave alternans identifies patients with ischemic cardiomyopathy who benefit from

- implantable cardioverter-defibrillator therapy. *J Am Coll Cardiol* 2007;49:50–8.
19. Gold MR, Ensley D, Chilson D, et al. T-wave alternans SCD HeFT study: primary endpoint analysis (abstr). *Circulation* 2006;114:II428.
 20. Bloch-Thomsen PE, HuiKuri HV, on behalf of the CARISMA Investigators. Cardiac Arrhythmias and Risk Stratification in Patients with Low Ejection Fraction after Acute Myocardial Infarction: The CARISMA Study (abstr). Paper presented at: Heart Rhythm Society Scientific Sessions; May 10, 2007; Denver, CO.
 21. Costantini O, Rosenbaum DS, Hohnloser SH, et al, for the ABCD Investigators. The Alternans Before Cardioverter Defibrillator (ABCD) Trial: a noninvasive strategy for primary prevention of sudden cardiac death using T-wave alternans (abstr). *Circulation* 2006;114:2426.
 22. Cantillon DJ, Stein KM, Markowitz SM, et al. Predictive value of microvolt T-wave alternans in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2007;50:166–73.
 23. Rashba EJ, Osman AF, MacMurdy K, et al. Enhanced detection of arrhythmia vulnerability using T wave alternans, left ventricular ejection fraction, and programmed ventricular stimulation: a prospective study in subjects with chronic ischemic heart disease. *J Cardiovasc Electrophysiol* 2004;15:170–6.
 24. Salerno-Uriarte JA, De Ferrari GM, Klersy C, et al. Prognostic value of T-wave alternans in patients with heart failure due to nonischemic cardiomyopathy: results of the ALPHA study. *J Am Coll Cardiol* 2007;50:1896–904.
 25. Sweeney MO, Ruetz LL, Belk P, Mullen TJ, Johnson JW, Sheldon T. Bradycardia pacing-induced short-long-short sequences at the onset of ventricular tachyarrhythmias: a possible mechanism of proarrhythmia? *J Am Coll Cardiol* 2007;50:614–22.
 26. Rashba EJ, Osman AF, MacMurdy K, et al. Influence of QRS duration on the prognostic value of T wave alternans. *J Cardiovasc Electrophysiol* 2002;13:770–5.
 27. Rashba EJ, Cooklin M, MacMurdy K, et al. Effects of selective autonomic blockade on T-wave alternans in humans. *Circulation* 2002;105:837–42.
 28. Ikeda T, Yoshino H, Sugi K, et al. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction. *J Am Coll Cardiol* 2006;48:2268–74.
 29. Ellenbogen KA, Levine JH, Berger RD, et al. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;113:776–82.

Key Words: defibrillator therapy ■ risk stratification ■ sudden death ■ T-wave alternans ■ ventricular arrhythmias.

▶ APPENDIX

For a list of persons and institutions who participated in the MASTER trial, please see the online version of this article.